UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,675	09/10/2003	Tim M. Townes	21085.0053U5	3735

23859 7590 10/11/2005

NEEDLE & ROSENBERG, P.C.
SUITE 1000
999 PEACHTREE STREET
ATLANTA, GA 30309-3915

EXAMINER	
LIETO, LOUIS D	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/659,675	TOWNES ET AL.	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/27/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

SD

DETAILED ACTION

Claims 1-24 are pending and currently under consideration.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the post office address of each inventor. A post office address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The post office address should also include the ZIP Code designation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 20 is rejected under the judicially created doctrine of double patenting over claims of U. S. Patent No. 5,877,288 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: a human hemoglobin. Claims 1-16 of U. S. Patent No. 5,877,288 encompass various recombinant human hemoglobins with anti-sickling activity. Therefore they are species of the broader genus of human hemoglobins claimed in claim 20 of the instant application. It is well established that a species of a claimed invention renders the genus obvious. In re Schaumann , 572 F.2d 312, 197 USPQ 5 (CCPA 1978).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "transgenic mouse whose genome comprises a human LCR γ-β hemoglobin switching DNA construct, wherein said genome is further homozygous for murine α- and β-globin knockout alleles such that said knockout alleles result in said mouse failing to synthesize murine hemoglobin, and wherein said hemoglobin switching construct is expressed such said mouse develops hemolytic anemia", does not reasonably provide enablement for a transgenic nonhuman mammal comprising erythrocytes that produce a human hemoglobin, but

fail to produce adult hemoglobin endogenous to said nonhuman mammal." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches the production of transgenic mice (adult HbS) who develop severe hemolytic anemia as a result of the production of human hemoglobin in the absence of murine hemoglobin, thus, providing a mouse model that closely approximates the fetal to adult globin genes in man. Applicants teach that the construction and use of a DNA switch construct is necessary to delay hemoglobin switching and prevent potential perinatal lethality. See page 25, lines 10-14. Applicants teach "how to use" the HbS mice as models for sickle cell disease because these mice develop significant *in vivo* pathology at a relatively young age under ambient conditions. Furthermore, Applicants teach "how to use" the transgenic mice of the invention according to its phenotype, the development of hemolytic anemia. Applicants report that "hemolytic anemia develops during the first few weeks of life as the level of HbF declines in these mice," and that "this temporal pattern of onset mimics the onset of anemia in human sickle cell infants during the first few months of life." See page 28, lines 13-19. As such, the specification teaches "how to make" transgenic mice whose genome comprises the essential DNA switch construct as well as knockout mutation in the endogenous α- and β-globin genes such that no murine hemoglobin is produced, such that one of skill would know "how to use" the transgenic mouse which develops the corresponding phenotype, hemolytic anemia.

With regard to the scope of the claimed invention, Applicant's claims are directed to transgenic non-human mammals whose genome comprises knockout mutations in endogenous globin genes. As such, the specification discloses the technology of making transgenic mice

utilizing embryonic stem (ES) cells. However, the prior art and post-filing art are replete with references which indicate that ES cell technology is generally limited to the mouse system, at present, and that only "putative" ES cells exist for other species. See Moreadith et al. (J. Mol. Med., 1997), page 214, Summary. In addition, Seamark (Reproductive Fertility and Development, 1994) discloses that totipotency of ES cell technology in many livestock species has not been demonstrated (page 6, Abstract). Mullins et al. (Journal of Clinical Investigation, 1996) disclose that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated" (page S38, col. 1, first. parag.). As the claims require introduction of a knockout construct into an ES cell, the state of the art supports that only mouse ES cells were available for use for production of transgenics.

Furthermore, the claimed invention is directed to transgenic nonhuman mammals whose genome comprises a human globin transgene(s). However, without evidence to the contrary, transgene expression in different species of transgenic nonhuman mammals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). This observation is specifically supported by Hammer et al. (Journal of Animal Science, 1986) who report the production of transgenic mice, sheep and pigs, however only transgenic mice exhibited an increased growth due to the express of the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. See also Ebert et al. (Molecular Endocrinology, 1988). The observation is further supported by Mullins et al. (Journal of Clinical Investigation, 1996) who report on transgenesis in the rat and larger mammals.

Mullins et al state that "a given construct may react very differently from one species to another." See page S39, Summary. Wall also supports this observation by stating "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. Wall further reports, "transgenic expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies." See page 62, first paragraph. Kappel et al (Current Opinion in Biotechnology, 1992) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from Differential CpG methylation (page 549, column 2, 3rd full paragraph). Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, including pigs and rabbits, because for example, the cis acting elements may interact with different trans-acting factors in these other species (paragraph, bridging pages 238-239). Given such species differences in the expression of a transgene, it would have required undue experimentation to extend the results achieved in transgenic mice to the levels of transgenic product in any other transgenic nonhuman mammal, the consequences of that production, and therefore, the resulting phenotype.

Furthermore, it is emphasized that transgenic elements such as promoter, enhancer, coding and non-coding sequences, presence or absence of introns, etc., are all determining factors in the production of transgenic nonhuman mammals, wherein the transgene is expressed at a level sufficient to convey a correlative phenotype. e.g., hemolytic anemia. The phenotype renders the animal useful as taught by the specification, i.e., the specification teaches "how to use" the transgenic animals as models for sickle cell disease. As such, the issue here is that

applicants fail to teach or provide a clear correlation for "how to make" a transgenic nonhuman mammal, other than a mouse, using a transgene comprising any human globin gene, wherein the animal expresses the transgene at levels sufficient for 'how to use" it as taught by the specification. Thus, as unpredictable transgene behavior is supported by the cited references above, the state of the art at the time of filing cannot be relied upon to provide the nexus between the exemplified HbS mice and other transgenic nonhuman mammals.

With regard to the enabled scope of human hemoglobin transgene, applicants provide evidence of the necessity utilizing a DNA "switch construct" for the generation of the transgenic mice of the invention. Applicants report that the precise regulatory sequences that control human γ- to β-globin gene switching are unknown, but suggest that the LCR γ-β transgene contains most if not all of the necessary sequence for correct switching. See page 21, lines 24-27. Applicants fail to teach such a "switching" effect from any other regulatory sequence or region, or even that any other regulatory region would have such "switch" function. As such, the courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. *Ex parte Maizel*, 27 USPQ2d 1662 (BPAI 1992). Therefore, the claims should be specifically limited to comprise at least those necessary elements of the disclosed DNA switch construct, the LCR γ-β transgenic, as applicants appear to provide evidence that their results are unexpected.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction or guidance provided by the specification, the absence of working examples for the demonstration or correlation to the production of transgenic nonhuman mammals of more than one species expressing a human γ-β globin "switch" transgene

as well as comprising endogenous knock out mutations of the α- and β-globin genes, in particular, in view of the underdeveloped state of the ES cell art, at the time of filing, for species of mammals other than mice, the unpredictable state of the art with respect to the generation of transgenic non-human mammals of al species expressing identical levels of a transgene and developing identical phenotypes due to such expression, and the breadth of the claims, it would have required undue experimentation of one skilled in the art to make and/or use the claimed invention as broadly claimed with a reasonable expectation of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (f) he did not himself invent the subject matter sought to be patented.

It is noted that claim 20 is a product-by-process claim. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made

by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted).

The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Claim 20 is rejected under 35 U.S.C. 102(b) as being anticipated by Dong et al. {Dong et al. (February 1995) Arch. Biochem. And Biopys. 316:893-898}.

Dong et al. provides guidance on the purification of human hemoglobin (Abstract; pg. 894, col. 1, Materials and Methods). Thus, by teaching all the limitations of the claims as written, Dong et al. anticipates the instant invention as claimed.

Claim 20 is rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 5,877,288 (3.2.1999) priority to (6.21.1993).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the

inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

US Patent No. 5,877,288 provides guidance on a human β-globin with anti-sickling activity (Claims 1-6). This protein meets all of the limitations of claim 20 of the instant application. Thus, by teaching all the limitations of the claims as written, US Patent No. 5,877,288 anticipates the instant invention as claimed.

Claim 20 is rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

It is noted that the applicant has not filed any information on the assignment of the instant application; therefore ownership cannot be determined. Further, the inventors of US Patent No. 5,877,288 include Tim M. Townes and Steven L. McCune. Steven McCune is not listed as an inventor of the instant application.

US Patent No. 5,877,288 provides guidance on a human β-globin with anti-sickling activity (Claims 1-6). This protein meets all of the limitations of claim 20 of the instant application. Thus, by teaching all the limitations of the claims as written, US Patent No. 5,877,288 anticipates the instant invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paszty et al (Ref. A24) and Ciavatta et al (Ref. A9) taken with Rubin et al (Ref. A29) and Fabry et al (Ref. A12).

The claimed invention is directed to transgenic nonhuman mammals comprising erythrocytes that produce a human hemoglobin, but fail to product adult hemoglobin endogenous to said nonhuman mammal.

Paszty et al. teaches the generation of knock out mice mutant for both adult α-globin genes. Paszty et al. teach rescue of the lethal phenotypes by introduction a human α-globin gene. Ciavatta et al. teach targeted deletion of mouse β^{maj}- and β^{min}- globin genes in mouse embryonic stem cells. Ciavatta et al. further suggests appropriate matings between α-thalassemic mice and mice that synthesize high levels of human sickle cell hemoglobin (HbS) for the production of mice that synthesize HbS exclusively. See page 9262, col. 1. As such, at the time of the instant invention both Rubin et al. and Fabry et al. teach the production of transgenic mice expressing HbS and/or HbS-Antilles transgenes.

According, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to mate the α-globin mutant mice of Paszty et al. with the β-globin mutant mice of Ciavatta et al. to produce transgenic mice comprising knockouts in the endogenous globin genes which knocking in the human globin genes for rescue of the lethal phenotypes, or by mating the mice mutant for the endogenous globin genes with a transgenic

mouse expressing high levels of HbS with a reasonable expectation of producing a transgenic mouse production human hemoglobin in the absence of the production of endogenous hemoglobin.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of results to the contrary.

Claims 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paszty et al and Ciavatta et al taken with Rubin et al and Fabry et al, as applied to claims 1-19 above, and further in view of Westphal (FASEB J, 1989).

The combination of Paszty et al and Ciavatta et al taken with Rubin et al and Fabry et al do not specifically suggest using the mouse models for screening methods, although they suggest creating better models for sickle cell disease (see pages 9262, col. 2 of Ciavatta et al.). However, at the time the claimed invention was made, Westphal et al. teach that the potential use of homologous gene targeting for biotechnology becomes obvious if we think about the genes that are affected in human genetic disorders. Specifically, Westphal discuss that mice carrying specific globin gene defects would be invaluable in designing remedies and screening drugs for the most frequent of all serious human disorders, thalassemia and sickle cell anemia. See page 120, column 1, 3rd paragraph.

Accordingly, in view of the teachings of Westphal, it would have been obvious for one of ordinary skill in the art to utilize the transgenic mouse models of the combination of Paszty et al., Ciavatta et al., Rubin et al., and Fabry et al. for designing remedies and screening drugs with a reasonable expectation of success.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of results to the contrary.

No claims allowed.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Dr. Louis D. Lieto
Patent Examiner
Art Unit 1632

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800 1630